LOS ANGELES COUNTY DEPARTMENT OF HEALTH SERVICES

TB TIMES

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Is There Interest in TB Drug and Vaccine Development?

"The failure to develop measures to prevent tuberculosis everywhere threatens our ability to control the disease anywhere, including in the United States." —A.M. Ginsberg

As the focus of tuberculosis elimination expands internationally, the demand for developing more effective vaccines and anti-tuberculosis drugs becomes increasingly apparent. Despite the tremendous global burden caused by TB, there has been no new anti-tuberculosis drug development in over twenty-five years. Directly Observed Therapy short-course (DOTS) has been shown to have a 95% cure rate. However, it is labor-intensive and is currently available to only 12% of patients with active disease worldwide. The BCG vaccine, although effective at preventing disseminated and meningeal TB in children, has questionable efficacy ranging from 0% to 77% protection. The need for better interventions is clearly evident in light of the goal of TB elimination by the year 2010 in the United States. Recent reports by the World Health Organization's (WHO) STOP TB Initiative and the Special Program for Research and Training in Tropical Diseases, in addition to a supplemental edition in Clinical Infectious Diseases on the Blueprint for Tuberculosis Vaccine Development Workshop, spotlighted the issues surrounding the creation of new drugs and vaccines to help fight TB.

WHO interviewed 36 employees from 19 of the top pharmaceutical companies in an effort to understand the barriers to anti-tuberculosis drug development. The primary disincentive stated by all individuals was cost. To formulate a new drug from laboratory work through clinical trials requires a $300 to $500 million investment. Unfortunately for TB, the perceived returns are minimal considering that major markets exist primarily in developing countries. The goal is to reach, at minimum, $200 to $300 million in annual sales after three to five years but, not surprisingly, TB drugs currently provide only $100 million in annual estimated peak sales. Companies also consider the cost of having scientists work on anti-TB drug research when they could be developing drugs for cancer or more marketable health problems. As quoted by one pharmaceutical representative, "All companies have limited resources. If you have to decide which drug to discover, you will try to choose those areas that provide a return where there is less competition, high volume and price where you can get your return back fast. You will be looking at cancer, hypertension, Alzheimer's, or cen-

Upcoming Conferences

- December 1, 2000 9:00 a.m. - 10:30 a.m.
  Orthopaedic Hospital - Andrew Norman Hall
  "Treatment Guidelines for Management of Latent Tuberculosis Infection (LTBI)"
  Paul Davidson, M.D., Director, TB Control Program

  10:30 a.m. - Noon
  Orthopaedic Hospital - Andrew Norman Hall
  Physician Case Presentation
  Vincent Hsu, M.D.

- December 5, 2000 8:00 a.m. - Noon
  TB Control Program Headquarters, Room 506 A
  "TB 101" Train the Trainer for Community Health Workers
  Robert Miodovski, M.P.H., Senior Health Educator
  (Pre-registration required - please call 213-744-6229 for information)

- December 14, 2000 8:00 a.m. - 4:30 p.m.
  TB Control Program Headquarters, Room 506 A
  Nursing Intensive - "TB 101"
  (Pre-registration required - please call 213-744-6229 for information)

- December 15, 2000 9:00 a.m. - 11:30 a.m.
  TB Control Program Headquarters
  Physician Case Presentation

Save The Date

- December 6, 2000 9:00 a.m. - 4:00 p.m.
  Santa Clara Convention Center - San Jose, California
  Tuberculosis Update Course
  Sponsored by the Francis J. Curry National TB Center
  For more information or to register for this free course, please call (415) 502-4620

tral nervous system disorders. Tuberculosis—maybe somebody else will think about tuberculosis. A company would be impacted dramatically if tuberculosis became a real concern in the United States or Western Europe."

Individuals also brought up the issue of a perceived lack of medical need since the advent of DOTS. Consequently, companies do not sense a compelling reason for market entry. Most feel that since there are effective and inexpensive TB drugs already available, a new drug would have to be priced sufficiently lower and would only capture 10-20% of the market—an inadequate amount. Although multi-drug resistance offers a unique niche, the consensus is that MDR-TB is a problem of compliance and public health systems, thus making new drugs unwarranted.

Companies also express unease over political pressure coming from WHO and state, "WHO always wants cheap drugs but wants to have the pharmaceutical industry pay for developmental costs. WHO does not want to appear publicly aligned with companies, yet at the same time still wants companies to stick their neck out for WHO." Other issues include patent protection enforcement and the potential for parallel importing into the United States if cheaper versions were sold in less developed countries. Furthermore, concern that a new drug would be solely reserved for TB prevents interest in testing multi-purpose drugs for anti-TB activity.

There are other disincentives cited, separate from market concerns, such as the scientific challenge of eliminating an organism that is biologically difficult to treat, dangers of laboratory infection, and the difficulty of demonstrating single-drug success when TB requires a multi-drug regimen. Nevertheless, there was resounding consensus that a sound financial incentive would overcome the other existing barriers.

If you have to decide which drug to discover, you will choose those areas that provide your return fast. Tuberculosis—maybe somebody else will think about tuberculosis.

In response, the WHO has renewed its commitment to increase collaboration between the public and private sectors with the burden falling on the public sector to maintain interest. WHO understands that "finding substantive, affordable methods to pull industry into the anti-tuberculosis drug market will be a formidable task, requiring persistent efforts and considerable thinking outside the box. Ultimately, WHO will need to change both the market picture and industry's perception of the market picture."

Further successes include the formation of the Global Alliance for TB Drug Development, a not-for-profit coalition focused on accelerating the discovery and formation of TB drugs. Its creation heralds the advent of public-private sector collaborations required for advancing TB drug development. In spite of the latest ventures, the arrival of a new drug will not be available for at least another ten years. The Advisory Council for the Elimination of Tuberculosis (ACET-DHHS) adds that, "Tuberculosis elimination probably cannot be achieved in the United States without the development of an effective vaccine…the only hope for tuberculosis control throughout the world is an effective vaccine."

In March of 1998, ACET-DHHS, the National Vaccine Program Office (NVPO), and the National Institute of Allergy and Infectious Diseases (NIAID-NIH), met to discuss a strategy for creating effective TB vaccines. They concluded that recent scientific advances make creating more effective TB vaccines a feasible endeavor worthy of a significant na-

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Case Report Reminder

As the year rapidly draws to a close, TB Control would like to remind everyone to update their casework and to report all TB confirmations as soon as possible. **All cases need to be confirmed by December 31, 2000** in order to be accurately included in the case count for 2000. As of November 15, 2000, there were 112 culture positive TB suspects that were not confirmed. TB Control urges everyone to submit and/or follow-up any outstanding paperwork. If you have any questions about reporting, call TB Control at 213-744-6160.

WORLD TB UPDATE

A summary of selected TB news and journal articles compiled from the CDC HIV / STD / TB Prevention News Update

New funding, partnerships, and developments in TB research

In the past few months, several governmental organizations have provided new funding and alliances with non-governmental organizations. Through its new Challenge Grants program, the National Institute of Allergy and Infectious Diseases provides matching funds to companies who will commit their own dollars and resources toward developing new drugs and vaccines against malaria, TB, influenza and dengue. TB research from various companies will be directed toward efforts such as the development of second-generation anti-TB drugs based on the chemical structure of ethambutol, modification of thiolactomycin, and clinical testing of new candidate vaccines.

The Global Alliance for TB Drug Development, a public-private partnership inaugurated in October, is another organization dedicated to development of affordable anti-TB drugs in third-world countries. Funding sources include the Bill and Melinda Gates Foundation and the Rockefeller Foundation. The Global Alliance expects the first new drug to be registered by 2010.

A National Institute of Health study is allowing international scientists at the Los Alamos Lab in New Mexico to identify structures and shapes of about 400 proteins present in *M. tuberculosis* by crystallization techniques. Finally, new findings from researchers at the University of British Columbia and TerraGen Discovery in Vancouver show that tuberculosis (TB) has a weak spot. The teams discovered chemicals that inhibit bacterial enzymes called protein kinases. Testing a number of chemicals on Streptomyces, a bacterium distantly related to TB, showed that kinase inhibitors could stop bacterial growth. This new finding provides a broad base for developing new drugs for TB, as long as they do not interfere with human protein kinases.

Combination antiretroviral therapy significantly reduces risk of TB in HIV+ patients

The risk of contracting tuberculosis is significantly decreased among HIV-infected patients who receive combination antiretroviral therapy. That's according to results of an observational, multicenter, prospective cohort study published in the September 8th issue of the journal AIDS. In the paper, Italian investigators with the Gruppo Italiano di Studio Tubercolosi e AIDS, led by Dr. Enrico Girardi of Centro di Riferimento AIDS, in Rome, present results of 1360 subjects who completed tuberculin skin tests at baseline and started on double or triple combination antiretroviral therapy. Average follow-up was 2 years and 997 subjects completed the trial. Eighteen cases of TB occurred in the study population during follow-up. After the researchers adjusted for confounding factors including baseline tuberculin skin test status and CD4 count, the incidence of TB was reduced by roughly six times in subjects taking two antiviral drugs and 10 times in those taking three antiretrovirals compared with subjects on no therapy or monotherapy. Consistent with prior study results, Dr. Girardi's team found that tuberculin positivity and a low CD4 count were associated with an increased risk of TB, independent of antiretroviral therapy. The investigators believe, based on their findings, that the widespread use of combination antiretroviral therapy could result in a decrease in the incidence of HIV-related TB, which in turn could produce a reduction in the overall incidence of TB in the general population. *AIDS 2000; 14:1985-1991*.

Above threshold, size of TST does not predict active TB disease

It is a common belief that larger tuberculin reactions are more serious, and more likely to indicate patients with active tuberculosis (TB) or at high risk of disease in the future. Authors report that, among 182 close contacts, and 502 patients suspected of possible active TB, 529 underwent tuberculin skin testing (TST) and 605 had a chest radiograph. They say the final diagnoses, based on all available clinical, microbiological, histological, and radiographic information, were: active TB, 68; inactive TB, 274; nontuberculous mycobacterial disease, 14; conditions associated with anergy, 36; no detectable abnormality (except a positive TST) or condition unrelated to TB, 213; and negative TST, no further evaluation, 79. Among these patients, they noted TST of 5 mm or larger was significantly more likely to indicate active or inactive TB ($p < 0.001$). However, they

report that, among patients with TST of 5 mm or greater, the size and frequency distribution of tuberculin reactions were not different between subjects with different diagnoses, nor between subjects with different types or extent of radiographic findings. They also noted that TST reactions were no different in 121 subjects with or 176 subjects without a history of BCG vaccination. They comment that, in close contacts or patients suspected of active TB, reactions less than 5 mm indicated lower likelihood of active or inactive disease, but above that threshold, size of tuberculin reaction did not matter. *American Journal of Respiratory and Critical Care Medicine 2000; 162: 1419-1422*

Social factors, HIV infection contributes to hospitalization of TB patients

This prospective cohort study followed 1493 TB patients from diagnosis to completion of therapy at 10 public health programs and area hospitals in the US. The study examined the costs, lengths of stay and patient characteristics associated with TB hospitalizations. The main outcome measures used for the study were the following: 1) occurrence, 2) cost, and 3) length of stay of TB-related hospitalizations. Authors report that there were 821 TB-related hospitalizations among the study participants; 678 (83%) were initial hospitalizations and 143 (17%) were hospitalizations during the treatment of TB. Patients infected with human immunodeficiency virus (HIV) (OR 1.8 95%CI 1.2-2.6), and homeless patients (OR 1.7 95%CI 1.1-2.8) were at increased risk of being hospitalized at diagnosis. They note that homeless patients (RR 2.5, 95%CI 1.5-4.3), patients who used alcohol excessively (RR 1.9, 95%CI 1.2-3.0), and patients with multidrug-resistant TB (RR 5.7, 95%CI 2.7-11.8) were at increased risk of hospitalization during treatment. They found the median length of stay varied from 9 to 17 days, and median costs per hospitalization varied from $6 441 to $12 968 among the sites. They conclude that important social factors, HIV infection, and local hospitalization practice patterns contribute significantly to the high cost of TB-related hospitalizations and call for additional efforts to address these specific factors in order to reduce the cost of preventable hospitalizations. *International Journal of Tuberculosis and Lung Disease*; 2000; 4 :931-939

Managing MDR-TB is ten times the cost of sensitive TB

Multidrug resistant tuberculosis (MDR TB) requires a complex drug regimen and lengthy multidisciplinary care; the financial cost of successful management of each case is potentially large. These authors compared the costs

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Pomona Creates Successful Home Detention Program

Over the past twelve months, staff at Pomona Health Center have worked together to create an effective plan for monitoring individuals on home detention. The plan addresses the manner in which district telephone and visual monitoring will be conducted for an incurable or chronically smear positive patient who is isolated to his or her home per court order. The plan specifies that daytime, weekend, and after-hours visits to the individual's home will be conducted by Public Health Investigators, Public Health Nurses, or Community Workers for the purpose of monitoring the individual's adherence to the terms and conditions of the court order. Additionally, the plan is designed so that there is a degree of randomness which cannot be anticipated by the detainee.

We know that Pomona Health Center staff have put a lot of thought and effort into creating a plan that not only works well for district staff, but also protects the public health in the best possible way. We want Pomona staff to know that the effort they have put into monitoring the individual that is currently detained at home is greatly appreciated. In particular, the addition of evening and weekend monitoring is essential to the effective monitoring of individuals on court-ordered home isolation. We would like to acknowledge the efforts of all Pomona staff who contribute to the management of problem patients. However, we would like to thank the following individuals in particular for their efforts: Dr. Lillian Lee, Medical Director; Christine White, PHI; Deborah Prada, PHN; Clara Tyson, PHNS; and Diane Rogers, Nurse Manager. Great job!

Paul Davidson, MD

from page 2, TB Vaccine

tional and international effort. With the genetic sequencing of the tubercle bacillus, new vaccine targets have been discovered and, in a short time, 50-100 candidate vaccines have been developed to the stage of evaluation in animal models. At this point, however, there is poor understanding of the immune response necessary for protection against disease. The correlate of immunity has not been found and further basic science research is needed before a successful vaccine can be formulated. Nevertheless, long-term support is finally a possibility as there is increased interest in TB research at both the National Institutes of Health (NIH) and at the Centers for Disease Control and Prevention (CDC).

Ultimately, TB vaccine development will require sustained commitment and extensive interdisciplinary collaboration between participating governments, scientists, vaccine manufacturers, and health care personnel both within the United States and internationally.

Meera Sreenivasan

References

1. WHO. Incentives and Disincentives for New Anti-Tuberculosis Drug Development. *Revision 1999*.
2. Ginsberg. A Proposed National Strategy for TB Vaccine Development. *CID 2000;30(Suppl 3):S233-42*.
3. http://www.tballiance.org.

Happy Holidays from all of us at TB Times!

from page 4, World TB Update

of managing nine HIV negative patients with pulmonary MDR TB with 18 age group and ethnicity-matched controls with fully sensitive disease. Their calculations included: cost of outpatient visits and inpatient stays including negative pressure isolation; costs of drug provision and toxicity monitoring; costs of additional procedures and multidisciplinary referrals. They report the mean cost of managing a case of pulmonary MDR TB was in excess of £60 000 (US$84 000) and for sensitive disease it was £6040 (US$8460). Authors comment that clinicians and healthcare commissioning authorities may both be underestimating the costs of managing MDR TB, and accordingly the consequences for units dealing with such cases may be serious. They say funding of care for MDR TB in the UK requires strategic decisions at regional or governmental level. *Thorax 2000; 55:962-963*

CDC to revise guidelines for prevention of TB transmission in healthcare facilities

The Advisory Council for the Elimination of Tuberculosis (ACET) of the US Centers for Disease Control and Prevention is revising the existing 1994 Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Healthcare Facilities, to modify recommendations for screening healthcare workers for TB. The goal of the ACET, which has met regularly since July 2000, is to simplify and clarify existing guidelines. For example, it is difficult to apply general national guidelines for skin testing to small community hospitals that have never had a single TB case, Dr. Amy Curtis, chair of the work group, commented during its latest meeting. The committee seeks to devise a better method of determining the frequency and type of skin test used in various environments. Because skin testing often produces false positive results, accurate guidelines are needed to avoid unnecessary expense and concern. In addition, the two products used for skin testing, Aplisol and Tubersol, have differing rates of false-positive results, a finding which requires additional study, ACET committees members noted. The work group will focus on recommendations for periodic tuberculin skin tests in low prevalence facilities, inclusion of non-hospital settings in the guidelines, expansion of laboratory information, update of engineering controls and personal respiratory protection. A draft document will be available in the spring of 2001, with the final version scheduled for publication in two years. Dr. Curtis commented that the issues are as complex as they were in 1994 when the previous guidelines were published, and that the work group will need to consider diverse interests in establishing the new guidelines.

The Clinical Corner

Pregnancy and the Pulmonologist

A pulmonologist calls TB Control and states he is seeing a 39 year old woman from Vietnam who is near term with a second pregnancy. She was referred to him for cough. Chest radiograph showed a right middle lob infiltrate, and although the patient was treated with clarithromycin, she did not improve. Ten days later, a repeat chest radiograph was noted to be unchanged. Sputum for AFB was ordered, and was recently found to be smear-positive; culture is pending. The patient's usual nongravid weight is about 64 kg.

QUESTIONS:

1. The most likely diagnosis is:
   A. *M. avium* complex
   B. Pulmonary contusion
   C. Community acquired pneumonia
   D. Tuberculosis
   E. Aspiration pneumonia

2. The pulmonologist asks if labor should be induced before starting treatment to spare the fetus from any adverse effects of medication. You respond:
   A. Induce labor now and make sure all health care workers who are present at delivery wear appropriate respiratory protection.
   B. Wait until the patient delivers naturally, then start her on a regimen of at least INH, RIF, and EMB pending susceptibility results; be sure to add PZA after delivery.
   C. Begin treatment now with at least INH, RIF, and EMB pending susceptibility results; be sure to add PZA after delivery.
   D. Start the patient on oxygen.
   E. Start erythromycin.

3. Is there anything else you should recommend?
   A. Have the patient wear a surgical mask when she comes to her prenatal appointments.
   B. Order additional sputa for AFB smears and cultures.
   C. Send the placenta for AFB smear and culture after delivery.
   D. Assess the newborn after delivery for congenital TB
   E. All of the above

ANSWERS:

1. **D**

The patient was born in a county where TB is prevalent. She has no known risk factors for *M.avium* complex disease (e.g. underlying lung disease or immunodeficiency), pulmonary contusion (due to trauma), or aspiration pneumonia (e.g. history of alcoholism). Community acquired pneumonia would probably have responded to treatment with clarithromycin and would not likely have presented with positive AFB smears of her sputa.

2: **C**

INH, RIF, and EMB are safe to use in pregnancy. While the TB Control Manual for L.A. County and some international organizations recommend the use of PZA along with INH, RIF, and EMB in pregnancy, other experts would not use PZA because its teratogenic risks are unknown (*Am J Resp Crit Care Med 1994; 149: 1359-74*). Inducing labor now is unnecessary and would expose health care workers to an infectious patient for no good reason. Withholding treatment will prolong this patient's infectious period and leave her fetus at risk for congenital TB. If she is still infectious at delivery, the patient will be an infectious risk to health care workers and her newborn. There is no indication for oxygen. Erythromycin is unnecessary, and clarithromycin (a related drug) did not improve the patient's condition

3. **E**

The patient's positive sputa smears indicate she is currently infectious; she should wear a surgical mask to her prenatal appointments and be seen in a time and place where she would expose as few persons as possible. Additional sputa for AFB should be ordered to monitor her infectiousness. Finally, although congenital TB is rare, the placenta and infant should be assessed for evidence of vertical TB transmission which can occur.

Postscript: This case is based on an actual telephone consultation. The patient was started on anti-TB treatment while pregnant and her sputa smear converted to negative before she went into labor. She and her infant did well.

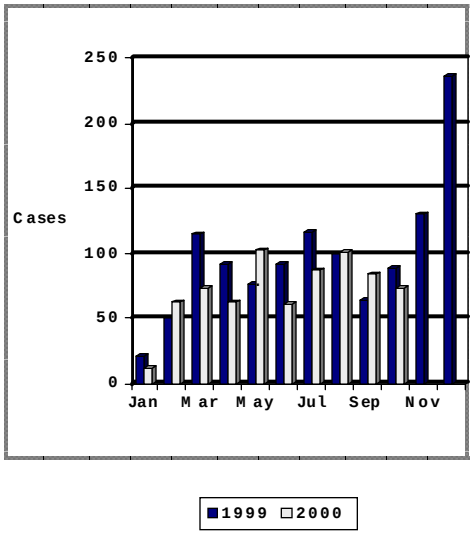
Annette Nitta, MD

Tuberculosis Cases by Health District
Los Angeles County, October 2000
(Provisional Data)

Service Area	Service Area Total Year to Date	Health District	Oct-00	Oct-99	Year to Date 2000	Year to Date 1999
SPA 1	7	Antelope Valley	0	1	7	16
SPA 2	103	East Valley	1	4	21	33
		West Valley	2	4	44	39
		Glendale	1	3	23	18
		San Fernando	0	0	15	21
SPA 3	121	El Monte	2	9	40	51
		Foothill	1	1	13	13
		Alhambra	7	5	45	50
		Pomona	2	3	23	19
SPA 4	185	Hollywood	5	5	62	76
		Central	17	3	89	84
		Northeast	3	4	34	45
SPA 5	24	West	5	3	24	26
SPA 6	115	Compton	1	4	23	27
		South	2	3	23	22
		Southeast	0	1	21	19
		Southwest	5	8	48	49
SPA 7	87	Bellflower	3	10	27	36
		San Antonio	3	5	32	33
		Whittier	2	3	11	23
		East Los Angeles	4	3	17	21
SPA 8	70	Inglewood	3	5	32	42
		Harbor	3	0	12	9
		Torrance	1	2	26	31
Unassigned	4	Unassigned	0	0	4	5
TOTAL	716		73	89	716	808

Los Angeles County Tuberculosis Incidence

By Month of Report, 1999-2000



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TB Times is a monthly publication providing information to those interested in TB surveillance and TB Control Program activities. Please forward your articles, comments, suggestions or address corrections to:

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